Remarks

In reply to the Office Action dated October 30, 2006, Applicants submit this Amendment and Reply. With this Amendment, claims 34, 38, 40, 53, and 55-56 have been amended. Upon entry of this Amendment and Reply, claims 34-40, 53 and 55-56 will be pending. Applicants would like to thank the Examiner for her gracious participation in the February 13, 2007 telephonic interview.

Claim Rejections - 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 34-40, 53 and 55-56 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that no members of the claimed genus of genetic variations or SNPs associated with a patient's response to treatment with a compound have been described in terms of a particular nucleotide sequence or location within the genome. Additionally, the Examiner alleges that no compounds have been defined by their chemical structure or specific function. The Examiner further alleges that the specification does not exemplify any compounds that exhibit zero toxicity and whose activity is correlated with the occurrence of a genetic variation in a patient population. Applicants respectfully traverse the Examiner's rejection. Also, with this Amendment, claims 34, 38, 40, 53, and 55-56 have been amended to further clarify the invention.

Applicants note that the present application is directed to methods of formulating, methods of treating, and methods of preparing. Namely, the present application is directed

to method claims, not compositions or compounds. Therefore, the specification as filed adequately describes the present invention.

While the examples recited in the present application list hypothetical drugs A, B, C, D, and E rather than providing a list of actual specific drugs as well as specific SNPs, the examples are quite specific as to the methods to be used in identifying the desired compositions to treat a pathology. It is these methods that are the heart of the present invention. Therefore, the use of specific therapeutics and specific SNPs would not provide additional knowledge nor would they serve any purpose in disclosing the present invention.

In essence, the present invention describes an investigational method for identifying various therapeutic compositions, not the specific compositions themselves. Therefore, the present invention is providing one skilled in the art with a means of ascertaining specific therapeutics that may be useful to a specific patient population. Answers to what exactly the therapeutic is, what specific SNP is being used, what specific patient population is being treated, and examples of compounds with no toxicity would provide no further guidance to one skilled in the art, in relation to the present invention.

Rather, Applicants respectfully submit that one skilled in the art would be able to take the methodology recited in the present invention and apply it to various "real-world" applications. Therefore, the application uses hypothetical elements rather than specific elements to illustrate the use of the claimed methods.

The discovery and development of various methodologies have been the cornerstone of the emergence of the biotechnology industry. Method technologies have changed the face

of pharmaceutical research, allowing innovative new drugs to be discovered and developed in a fraction of the time that might have been required otherwise. Development of innovative new methods is an expensive undertaking. Entire sub-industries in biotechnology have been formed that are comprised of companies having a method rather than a specific product or drug as their platform technology. Accordingly, companies with a method technology platform have relied on patent protection to obtain sufficient capital for their invention.

In the present invention, Applicants believe that a precise methodology for use in identifying and developing treatments for specific pathologies in specific sub-populations is disclosed. Applicants respectfully request the Examiner to look at Examples I and II of the present application.

Applicants respectfully point out that many patents have been issued by the USPTO which contain language very similar to the present application. For example, U.S. Patent No. 6,410,231 covers a method for detecting multiple single nucleotide polymorphisms (SNPs) in a population of target polynucleotides. Claim 1 of the '231 patent recites:

> A method for detecting multiple SNPs in a population of target polynucleotides in parallel, the method comprising the steps of:
> (a) combining sample polynucleotides; capture polynucleotides and SNP probes under conditions wherein:
> a subset of the sample polynucleotides are target polynucleotides, each comprising a different capture region and a different SNP region comprising a corresponding different SNP,
> the capture polynucleotides are immobilized and arrayed at corresponding discrete elements on a substrate and each capture polynucleotide comprises a sequence which specifically hybridizes to a corresponding different capture region,

each SNP probe comprises a sequence complementary to a corresponding different SNP region,
the target polynucleotides are immobilized by hybridizing to the capture polynucleotides whereby each target polynucleotide is immobilized at a corresponding discrete element of the substrate to provide a first discrimination of the sample polynucleotides, and
the relative affinity of each SNP probe for the corresponding SNP region is sufficient to provide selective hybridization of the SNP probe to the corresponding SNF region, whereby each SNP probe selectively hybridizes to the corresponding SNP region to provide a second discrimination of the sample polynucleotides; and
(b) detecting the presence of each SNP probe on the substrate, wherein the presence of a given SNP probe at a given element indicates the presence of the corresponding SNP in the corresponding target polynucleotide.

The language of claim 1 of the '231 patent is very similar to the language of the claims recited in the present application. Also, the present application in paragraphs [0025] and [0026] recite specific U.S. and WO patents and applications that relate to research methods to detect SNP variation in individuals and correlating that to a pathology and treatment. For example, please see U.S. Pat. Nos. 5,888,819; 5,547,835; 5,860,917; and 5,762,876.

Applicants believe that they have submitted evidence to justify the allowance of the claims as recited in the present application. Applicants have also amended claims 34, 38, 40, 53, and 55-56 to further clarify the invention. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Claim Rejections - 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 34-40, 53 and 55-56 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner alleges that the rejection is based on the breadth of the claims, the nature of the invention, the state of the

prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, and the quantity of experimentation necessary. Applicants respectfully traverse the Examiner's rejection. Also, with this Amendment, claims 34, 38, 40, 53, and 55-56 have been amended to further clarify the invention.

The present invention is directed to compositions of at least one compound that modulates the activity of a target molecule associated with a genetic variation. The modulation may consist of increasing or decreasing enzymatic activity, gene expression, interaction with other proteins, etc. The target molecule may have an activity that is directly affected by a compound or involved in the absorption, distribution, metabolism, or excretion of a compound. The target molecule in turn plays a role in the symptoms, etiology, or treatment of the pathology. Also, the term "associated" is defined in the specification as having any of a structure, activity, compartmentalization, degradation, secretion, etc., that correlates to a genetic variation.

As mentioned in the preceding pages, Applicants note that the present application is directed to methods of formulating, methods of treating, and methods of preparing. Namely, the present application is directed to method claims, not compositions or compounds. Therefore, the specification as filed discloses the exact subject matter recited in the claims and thereby enables one skilled in the art to reproduce the present invention. Applicants respectfully request the Examiner to look at Examples I and II of the present application.

While the examples recited in the present application list hypothetical drugs A, B, C, D, and E rather than providing a list of actual specific drugs or specific SNPs (genetic variation), they are quite specific as to the method to be used in identifying the desired compositions. It is this method that is the subject matter of the present invention. Therefore, the use of specific therapeutics and specific SNPs would provide no additional knowledge nor would they serve any further purpose. In essence, the present invention describes an investigational method for identifying various therapeutic compositions, not any one specific composition itself. Therefore, the present invention is providing one skilled in the art with a means of ascertaining a specific therapeutic that may be useful to a specific patient population suffering from a specific pathology.

Descriptions outlining what exactly the therapeutic is, what specific SNP is being used, what specific patient population is being treated, and examples of compounds with no toxicity would provide no further guidance to one skilled in the art. Rather, one skilled in the art would be able to take the methodology recited in the present invention and apply it to various "real-world" specific applications. The applications themselves can be better ascertained using hypothetical elements rather than defining any one specific element or its corresponding structural features, to illustrate the use of the inventive method. As such the claims cover the inventive method and are sufficiently disclosed in the specification. This would enable one skilled in the art to apply the present inventive method disclosed in the specification to specific situations.

The Examiner has also referenced the *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F. 3d 1316 (Fed. Cir., 2001). Relying on that case, the Examiner contends that the present invention is in a class of inventions characterized as "the unpredictable arts such as chemistry and biology." There are two reasons why the Mycogen case is distinguishable from the present situation. First, the case concerned art that had occurred in the 1980's. As the Examiner is surely aware, the state of the chemical and biological arts has advanced by leaps and bounds from 20 years ago. In many circumstances, what was unpredictable in the 1980's has become very predictable and reliable.

Thus, with regard to the present invention, methods to determining and characterizing SNPs that were generally available in the 80s were certainly readily available at the time the present application was filed. For example, in paragraphs [0025], the present application explains that "a genetic variation, such as a SNP, can be identified by finding a difference in the nucleotide sequence of an individual compared to the most common nucleotide sequence of the overall population. Methods used to identify genetic variations, such as SNPs, are well known in the art and include hybridization stability methods such as SSCP, where the hybrids are identified, for example, by electrophoretic analysis, denaturing HPLC (U.S. Pat. No. 5,795,976), or addressable DNA array hybridization (U.S. Pat. No. 5,547,839)."

Also, paragraph [0026] of the present application states "in accordance with the present invention, certain genetic variations are correlated with a pathology or treatment of a pathology. For example, the SNP encoding the change from normal hemoglobin to sickle

hemoglobin in sickle cell anemia. Methods for using a variety of patient determinants such as genetic variations to establish if one or more determinants are correlated with a pathology, or if one or more determinants are correlated with treatment of a pathology are known in the art and are exemplified in U.S. Pat. No. 5,860,917 and in publications such as WO 97/13875, WO 97/21833, WO 99/11822, WO 99/24571."

Secondly, and more importantly, the Examiner's reliance on the Mycogen case is not in parallel with the present situation. In fact the present invention actually lends support to the Mycogen court's decision. In Mycogen, the court opined that chemistry and biology are the unpredictable arts because results can be unpredictable. The present application concerns an inventive method which is intended to make that which is unpredictable (choosing the most effective combination of therapeutics for a specific pathology within a specific population) predictable. The present invention discloses a methodology (measuring a correlation of genetic variation within a target molecule) that when used, allows a physician to pinpoint at least one compound that provides the greatest percentage of efficacy in a particular patient population. Therefore, the reliance on Mycogen is respectfully distinguishable in the sense that the present invention is in support of what the court in Mycogen had concerns about. Namely, to try and make what is unpredictable, predictable.

The Examiner also alleges that guidance from the specification of the present application is missing concerning specific compounds, pathologies, target molecules, and SNPs. The Examiner states the novel aspect of the claims is the combination of compounds that modulate the activity of a SNP or genetic variation associated with a pathology.

However, the present invention is based on the methodology of identifying specific combination of compounds that modulate the activity of a SNP or genetic variation associated with a particular pathology within a particular population. The present invention is not based upon the specific combinations of compounds nor the specific SNPs themselves.

The Examiner also alleges that the art of identifying SNPs associated with a pathology in order to formulate a pharmaceutical composition is unpredictable. The Examiner goes on to state that a SNP occurs once every 1000 nucleotides in the human genome. The Examiner's assertion is not persuasive. Through the specification and the claims of the present application, a person of ordinary skill in the art is able to ascertain the specific SNPs associated with a specific pathology affecting a specific population.

The predictability of the claimed invention lies in the disclosed methodology, therein providing one skilled in the art with an aspect of predictability (how to treat a specific population afflicted with a specific pathology) to an otherwise unpredictable art (treating people afflicted with a disease). This further solidifies Applicants belief that outlining specific examples will not further clarify the present invention, hypothetical illustrations actually work better by allowing the reader to focus on the methods and uses, rather than the specific compounds, pathology etc.

The Examiner further alleges that the unpredictability of establishing a correlation between a polymorphism and a response to therapy is exemplified by the teachings of Wadler *et al.* (The Cancer Journal from Scientific American. 1997; 3:284-288). The Examiner alleges that although a ras mutation may be associated with the occurrence of a

disease, it remains highly unpredictable as to whether that mutation will be associated with a particular treatment. Applicants believe that the present invention lends predictability to this highly unpredictable field, and therefore is enabled.

The Wadler reference specifically deals with prognostic implications of c-Ki-ras2 mutations in patients with advanced colorectal cancer treated with 5-fluorouracil and interferon. The reference indicates that it is unlikely that ras2 mutations will have significant prognostic value to treatment regimens. Whether this is true or not, Applicants do not offer an opinion. However, the outcome of any study, much less one, has no bearing on the present invention.

Furthermore, as the Federal Circuit has explained, a claim may embrace some inoperable embodiments and yet still be enabled. See *CFMT, Inc. v. Yieldup Int'l Corp,*. 349 F.3d 1333 (Fed. Cir. 2003). The present invention provides a cost and time efficient method that enables one skilled in the art to go about finding meaningful relations, when they do exist.

The present invention provides a methodology to find those instances when there is a correlation between a specific mutation, a specific pathology, and a specific treatment. Applicants disagree with the Examiner that the art of identifying therapeutic compounds that modulate the activity of a molecule associated with a SNP is highly unpredictable. But even were this art unpredictable, the present invention provides a useful method to add predictability to the field.

For example, when scientists run a Blast search to identify a particular genetic variant within a library of genetic data. The search may prove fruitful, fruitless, or the results may be indeterminable. Yet the Blast search method is indeterminably valuable to sequence searching. As explained above, the present invention provides similar value to the field.

The Examiner also cites Lucentini (The Scientist. December 2004; page 20). Again, this reference alleges the unpredictability in the art of establishing an association between a mutation and the occurrence of a disease and a response to therapy. As noted above with the Wadler reference, the present invention is a method to enable one skilled in the art to find occurrences when there is a reliable and reproducible predictability. The present invention outlines a cost and time effective protocol to follow in the search for those instances when there is a correlation.

For example, the present application in paragraphs [0025] and [0026] recite specific U.S. and WO patents and applications that relate to research methods to detect SNP variation in individuals and correlating that to a pathology and treatment. Please see U.S. Pat. Nos. 5,888,819; 5,547,835; 5,860,917; and 5,762,876.

Applicants believe that they have submitted evidence to justify the allowance of the claims as recited in the present application. Applicants have also amended claims 34, 38, 40, 53, and 55-56 to further clarify the invention. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Claim Rejections - 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 34-40, 53 and 55-56 under 35 U.S.C. § 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter of the invention. With this Amendment, claims 34, 38, 40, 53, and 55-56 have been amended to further clarify the invention. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Claim Rejections - 35 U.S.C. § 102

The Examiner rejected claims 34 and 40 under 35 U.S.C. § 102(b) as being anticipated by Smith-Sorensen (British Journal of Cancer. 1998; 78: 375-381). The Examiner alleges that Smith-Sorensen teaches a method comprising the steps of measuring a correlation between a genetic variation in a target molecule in a population of patients and a response therapy and selecting two compounds with the greatest percentage of efficacy in the population. In particular, the Examiner alleges that Smith-Sorensen found that patients with TP53 mutations had a significantly better response to paclitaxel/cisplatin combination therapy as compared to cyclophosphamide/cisplatin therapy, wherein the response to therapy is considered to represent at least 1% of the total patient population. Finally, the Examiner alleges that in claim 34 the preamble of "formulating a pharmaceutical composition" and in claim 40 the preamble of "method of formulating a therapeutic composition" is not accorded patentable weight. Applicants respectfully traverse the Examiner's rejection.

The Examiner contends that this discloses the use of reference characterizes use of a specific genetic marker to determine which of two chemotherapy regimens were optimal for

long term survival. Both regimens involved treatment with cisplatin, which was then combined with either paclitaxel or cyclophosphamide. Despite Examiner's assertion, Applicants respectfully point out that the authors found NO statistically significant association between TP53 genotype, type of therapy, or treatment outcome. Thus, the Smith-Sorensen reference does not recite "measuring a correlation of genetic variation of a target molecule in said population with patient response to at least one compound known or suspected to treat said pathology," as recited in claim 34 of the present application.

Furthermore, the reference also does not disclose "(a) analyzing a target molecule in a patient population to detect SNPs associated therewith; (b) selecting a plurality of compounds having therapeutic efficacies correlated with the presence of at least one SNP associated with the target molecule, wherein said plurality is effective for at least 1% of the total patient population having said pathology" as recited in claim 40 of the present application.

The Smith-Sorensen reference plainly does not disclose the association between the agents/compounds, the genetic variation, and their relation to a specific pathology, as is recited in the claims 34 and 40 of the present application. Also, with this Amendment, claims 34 and 40 have been amended to recite "using the selected compounds to formulate the pharmaceutical composition" thereby reciting a use step in the body of the claim. In view of the foregoing, Applicants respectfully request that the Examiner withdraw this rejection.

Claim Rejections - 35 U.S.C. § 103

The Examiner rejected claims 35-39, 53 and 55-56 under 35 U.S.C. § 103 as being unpatentable over Smith-Sorensen in view of Pamukcu (U.S. Patent No. 6,235,776) and further in view of Masson (Clinical Pharmacokinetics. April 1997. 32(4): 324-343). The Examiner alleges that Smith-Sorensen teaches a method comprising the steps of measuring a correlation between a genetic variation in a target molecule in a population of patients and a response therapy and selecting two compounds with the greatest percentage of efficacy in the population.

The Examiner rejected claims 38-39, 53, and 55 under 35 U.S.C. § 103. The Examiner alleges that Smith-Sorensen does not teach treating the patients with paclitaxel and cisplatin following the detection of TP53 mutations, but that this would have been obvious to one of ordinary skill in the art at the time of the invention.

The Examiner rejected claims 35 and 56 under 35 U.S.C. § 103(a) as being unpatentable over Smith-Sorensen in view of Pamukcu. The Examiner alleges that Smith-Sorensen does not teach using a composition of three compounds to treat ovarian cancer patients but Pamukcu teaches methods for using three compounds to treat ovarian cancer patients using paclitaxel and cisplatin.

The Examiner rejected claims 36-37 under 35 U.S.C. § 103(a) as being unpatentable over Smith-Sorensen in view of Masson. The Examiner alleges that Smith-Sorensen does

not specifically teach that the pharmaceutical compositions exhibit minimal toxicity or no toxicity but Masson teaches that chemotherapeutic agents exhibit variable toxicity in patients and that toxicity is significantly effected by dose and treatment regimens.

Applicants respectfully traverse the Examiner's rejections. Also, with this Amendment, claims 34, 38, 53, and 55-56 have been amended to further clarify the invention.

As explained above, the Smith-Sorensen reference does not disclose "measuring a correlation of genetic variation of a target molecule in said population with patient response to at least one compound known or suspected to treat said pathology," as recited in independent claim 34 of the present application.

Likewise, Smith-Sorensen does not disclose "(a) analyzing a therapeutic target molecule in a population of patients having said pathology to detect SNPs associated therewith, wherein the target molecule contains a SNP, alters expression of SNPs, or is a member of a class of compounds that contain SNPs," as recited in independent claim 38 of the present application.

Smith-Sorensen does not disclose "(a) identifying a sub-population of patients having comprising at least one known SNP from all patients within the sub-population exhibiting said pathology; and (b) administering to said sub-population a composition comprising at least one therapeutic compound having an efficacy correlated with the presence of said SNP," as recited in independent claim 53 of the present application.

Finally, Smith-Sorensen does not disclose "(a) correlating the efficacy and/or toxicity of a first compound with the presence of one or more SNPs;(b) correlating the efficacy and/or toxicity of a second compound with the presence of one or more SNPs; (c) calculating the efficacy and/or toxicity of a said combination of said first compound and said second compound on said population of patients; and (d) combining said first compound and said second compound thereby preparing said combination of compounds for treating," as recited independent claim 55 of the present application.

Therefore, the Examiner has not established a prima facie case of obviousness. Moreover, the Examiner has not provided a reason or suggestion why the person skilled in the art would combine Smith-Sorensen with the cited secondary references. For this additional reason, applicants submit that the Examiner should withdraw this rejection. For the sake of argument, however, Applicants address the two secondary references below.

Regarding the Pamukcu reference, this reference describes a formulation for a combined chemotherapeutic reagent consisting of a known chemotherapy agent, paclitaxel, with an inhibitor of a new cyclic-GMP phosphodiesterase. There is no mention, however, of the use of genetic variants (for example, SNPs) to suggest the use of this combination. This correlation between pathology/therapeutic/and genetic variant is recited in independent claims 34, 38, 53, and 55, and it is not taught nor suggested, much less disclosed, by the Pamukcu patent.

Regarding the Masson reference, the Examiner cites this as prior art based on the author's discussion on the use of pharmacokinetics to anticipate proper dosage of chemotherapeutic agents to minimize toxicity. This concept is freely acknowledged in the background section of the present application. The Masson reference, however, does not teach or suggest, much less disclose, correlating the efficacy and/or toxicity of therapeutic compounds with specific genetic variants (for example, SNPs) within a specific population, as is recited in independent claims 34, 38, 53, and 55 of the present invention.

Dependent claims 35-37, 39, and 56 depend from independent claims 34, 38, 53, and 55 and therefore also are not taught or suggested by the prior art references. Because the references cited by the Examiner, alone or in combination, do not teach or suggest the claims as recited in the present application, Applicants respectfully request that the Examiner withdraw this rejection.

Conclusion

In view of the foregoing comments, Applicants respectfully request that the outstanding rejections be reconsidered and withdrawn. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that

personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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